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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,365	09/21/2005	Jean-Charles Quirion	QUIRION1	1397
1444 7590 10/31/2007 BROWDY AND NEIMARK, P.L.L.C. 624 NINTH STREET, NW SUITE 300 WASHINGTON, DC 20001-5303			EXAMINER KRISHNAN, GANAPATHY	
			ART UNIT	PAPER NUMBER
			1623	
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			10/31/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/522,365	<b>Applicant(s)</b> QUIRION ET AL.	
	<b>Examiner</b> Ganapathy Krishnan	<b>Art Unit</b> 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 03 August 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The amendment filed 8/03/2007 has been received, entered and carefully considered.

The following information provided in the amendment affects the instant application:

1. Claims 7-19 have been canceled.
2. Claims 1-4 have been amended.
3. Remarks drawn to objections to specification, claims and rejections under 35 USC 101, 112, first and second paragraphs, 102 and 103.

Claims 1-6 are pending in the case.

### ***Specification***

The objection to the specification for not having a section entitled, Brief Description of Drawings is being maintained for reasons of record. Applicants have filed a separate sheet with the title, "Brief Description of Drawings" to be inserted at page 8, line 20. Page 8, line 20 doesn't look like the appropriate page and line for the said insertion. Moreover, the figure number and a brief description of the figure should follow the said title.

Appropriate correction is required.

### ***Claim Objections***

The objections to Claims 2-3 have been overcome by amendment. The objections to claims 10-11 have been rendered moot by cancellation.

Art Unit: 1623

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The rejection of Claims 13-19 under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, has been rendered moot by cancellation of the claims.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 2-3 under 35 U.S.C. 112, first paragraph, has been overcome by amendment. The rejection of claims 10-11 has been rendered moot by cancellation of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 1-3 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been overcome by amendments.

The rejection of claims 7-19 has been rendered moot by cancellation of the claims.

Art Unit: 1623

The rejection of claim 6 has not been addressed by the applicants and is being maintained for reasons of record.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claims 1 and 3 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Quirion et al (Tetrahedron Letters, 2001, 42, 5879-5882; document # AE cited in IDS of 1/25/2005) is being maintained for reasons of record.

Applicants refer to the prior art reference used in this rejection by the first named inventor, namely Marcotte, instead of the last named inventor, namely Quirion. In the response below, the Examiner also uses the name Marcotte, instead of Quirion, for the sake of consistency.

Applicants have traversed the rejection arguing that:

The compounds as claimed in amended claim 1 and dependent claim 3 as well as in amended claim 4 are not disclosed or suggested by Marcotte, which concern the synthesis of new  $\alpha$ - and  $\beta$ -gem-difluoromethylene C-glycosides in the galactose and glucose series.

Applicants' arguments are not found to be persuasive.

Marcotte et al teach a C-glycoside (Structure 1, page 5879) that has a CF<sub>2</sub> group and an alkyl chain that is functionalized with an amine group and an acid function. Structure 1 of

Art Unit: 1623

Marcotte is a general structure. The stereochemistry of the protected hydroxyl groups in structures 8(a) and (b) and structures 10(a) and (b) are the same as in the structure in claim 1. Structures 8a-b and 10a-b are derived from general structure 1. The stereochemistry of the  $\text{CH}_2\text{OH}$  group attached to the 4 position of the pyranose ring in the said structures of Marcotte are indicated by wavy lines, which means that the stereochemistry is both up and down. The stereochemistry where the group is up reads on the instant structure.

Marcotte teaches that structure 1 is a glycoserine or glycothreonine (page 5879, right column, lines 8-9). The XO groups attached directly to the ring are either protected hydroxyls (if X is protecting group; same as Y, Y' and Y''' in instant structure of claim 1 wherein they are OR and R is Bn, Ac, etc.) or hydroxyl groups (if X is H; same as same as Y, Y' and Y''' in instant structure of claim 1 wherein they are OR and R is H). The  $\text{CH}_2\text{OX}$  to the left of the ring oxygen in structure 1 of Marcotte is same as  $\text{R}^3$  in instant structure for  $\text{R}^3 = \text{CH}_2\text{OGP}$  where GP is protecting group or is  $\text{CH}_2\text{OH}$ . In structure 1 of Marcotte, the ring carbon to the right of the ring oxygen bears a hydrogen. This is same as  $\text{R}^2 = \text{hydrogen}$  in instant claim 1.

Structure 1 of Marcotte also meets the limitations of instant claim 3 for the substitutions as explained above and wherein n is 1. The claim defines n as the number of  $(\text{CH}_2)$  units in the chain. In the absence of a numerical range for n it is interpreted as any integer.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

Art Unit: 1623

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of Claims 7-9 under 35 U.S.C. 103(a) as being unpatentable over Lerner et al (J. Org. Chem. 1979, 44(19), 3368-3373) in combination with Furstner (Synthesis, 1989, 571-590); the rejection of Claim 11 under 35 U.S.C. 103(a) as being unpatentable over Ullas et al (J. Med. Chem. 2002, 45, 1563-66; Published on the Web 3/14/2002) and the rejection of claim 12 under 35 U.S.C. 103(a) as being unpatentable over Quirion et al (Tetrahedron Letters, 2001, 42, 5879-5882; document # AE cited in IDS of 1/25/2005) in view of Wong et al (Bioorganic & Medicinal Chemistry Letters, 1998, 8, 2333-2338) made of record in the previous office action have been rendered moot by cancellation of claims 7-19.

The rejection of Claim 2 under 35 U.S.C. 103(a) as being unpatentable over Quirion et al (Tetrahedron Letters, 2001, 42, 5879-5882; document # AE cited in IDS of 1/25/2005) in view of Wong et al (Bioorganic & Medicinal Chemistry Letters, 1998, 8, 2333-2338) is being maintained for reasons of record.

Applicants refer to the prior art reference used in this rejection by the first named inventor, namely Marcotte, instead of the last named inventor, namely Quirion. In the response below, the Examiner also uses the name Marcotte, instead of Quirion, for the sake of consistency.

Applicants' have traversed the rejection arguing that:

1. The oxygen in the sugar ring is replaced by a CF<sub>2</sub> for miming oxygen and Wong does not suggest this solution.
2. The position of the peptidic chain is beta (rather than alpha as in Wong's) and the anomeric alcohol is alpha does not change the properties of the resulting molecule.

Art Unit: 1623

3. Applicants' solution cannot obviously result from the teaching of Wong and Marcotte due to the fact that at the time of the present invention Marcotte only disclosed a synthesis of gem-difluoromethylene C-glycosides by a cyclization using an intramolecular oxymercuration and such a solution is prohibited for medical purposes. Marcotte teach that they are studying a new method of cyclization to avoid the use of mercury salts. For this reasons Marcotte cannot be combined with Wong.

Applicants' arguments are not found to be persuasive.

According to Marcotte replacement of the anomeric oxygen with a gem difluoromethylene group induces differences in the biological functions of compounds of structure 1, which are also hydrolytically stable. Hence, preparation of new derivatives comprising a gemdifluoromethylene group in the place of anomeric oxygen is a promising avenue for the preparation of new glycoconjugate derivatives (page 5879, left column, lines 7-14). Hence, Wong need not necessarily teach the same concept. Marcotte et al teach a C-glycoside (Structure 1, page 5879) that has a CF<sub>2</sub> group and an alkyl chain that is functionalized with an amine group and an acid function.

Wong et al, drawn to C-glycosides, teach sugar derivatives of structural formula 3-8 (page 2334) that are structurally very close to the compound as instantly claimed. According to Wong these structures are useful as mimics of sialyl lewis X as inhibitors of E- and P-selectin (page 2333, abstract and first paragraph). In the structures of Wong, the anomeric carbon is attached to a CH<sub>2</sub>, which is attached to a carbonyl, which is attached to a nitrogen. This is the same type of attachment seen in the structure recited in instant claim 2. Since the structures of Wong according to him are useful mimics, one of skill in the art would want to replace the CH<sub>2</sub>



Art Unit: 1623

group by a  $\text{CF}_2$ , which would also mimic the oxygen as instantly claimed and as taught by Marcotte. One of skill in the art would extend this structural modification to other sugars too.

Marcotte and Wong are combinable and do render the instant claim obvious. Applicants' argument regarding the method of cyclization and its prohibition is not relevant since the claim is just drawn to a compound and not to a method of making it.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make compounds of structural formula as claimed in instant claim 2 since structurally similar compounds are taught in the prior art to have important biological activity.

One of ordinary skill in the art would be motivated to make the compounds and their compositions as instantly claimed since structurally similar compounds comprising the gemdifluoromethylene group directly attached to the anomeric carbon are hydrolytically stable (as taught by Marcotte) and the non halogenated analogs show E- and P-selectin binding inhibition, which is important for treatment of inflammation (as taught by Wong). One of ordinary skill in the art would thus be motivated to make compounds as instantly claimed in order to look for derivatives that are good inhibitors of the said selectins.

The rejection of Claims 4-6 under 35 U.S.C. 103(a) as being unpatentable over Lerner et al (J. Org. Chem. 1979, 44(19), 3368-3373) in combination with Furstner (Synthesis, 1989, 571-590) is being maintained for reasons of record.

Applicants have traversed the rejection by arguing that the combination of Lerner and Furstner does not teach a reaction in the presence of zinc at reflux of THF acting as a solvent or in the presence of a lanthanide derivative, between a lactone of the formula recited in claim 4 and

Art Unit: 1623

a halogenated derivative of general formula  $\text{XCF}_2\text{CO}_2\text{R}^8$ , wherein X is a halogen and  $\text{R}^8$  is an alkyl group so as to obtain an ester function which can be either reduced to alcohol and then oxidized into an aldehyde or hemi acetal or directly reduced to an aldehyde.

Applicants' arguments are not found to be persuasive.

Lerner teaches a method of preparing a sugar that is structurally very similar to the one instantly claimed, wherein a sugar lactone (structure 1 in scheme I, page 3369) is reacted with  $\text{BrCH}_2\text{COOEt}$  (similar to the halogenated derivative  $\text{XCF}_2\text{COOR}^8$  where X is a halogen as instantly claimed) via the Reformatsky reaction induced by zinc (page 3369, right column, scheme I and the first full paragraph below; page 3372, left column first full paragraph). This reaction produces a product that has structural features on the anomeric carbon, close to that as instantly claimed. The only difference is that, instead of a  $\text{CF}_2$  there is a  $\text{CH}_2$  group. But one of skill in the art will recognize from this teaching that the chemistry is still the same and can be applied in the reaction of  $\text{XCF}_2\text{COOR}^8$  with the sugar lactone as instantly claimed. At page 3372 (left column, first paragraph), Lerner discloses that the reaction was carried out by heating the lactone and ethylbromoacetate in dioxane. Substituting dioxane with THF is well within the skill level of the artisan since THF is also an ether (a cyclic monoether) like dioxane (cyclic diether).

Furstner teaches the use of lanthanides like samarium diiodide in the Reformatsky reaction (page 587, right column, last two lines). This means that the Reformatsky reaction as taught by Lerner can be carried out using samarium instead of zinc.

However, both Lerner and Furstner do not teach the use of a halogenated derivative having the formula  $\text{XCF}_2\text{COOR}^8$  wherein a gemdifluoromethylene group is present,

Art Unit: 1623

deoxygenation and the reduction of the ester function to an alcohol or reduction to and then further oxidation to an aldehyde or hemiacetal.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the sugar derivatives via a process as instantly claimed since such a process for making structurally close analogs using the same process is seen to be taught in the prior art.

One of ordinary skill in the art would be motivated to use the process as instantly claimed since it is mild and is seen to tolerate protecting groups on the sugar ring and gives reasonably good yields of the desired product. Further manipulations of the ester group is well within the skill of the artisan and one would be motivated to do such further manipulations in order to functionalize the alkylester group with other groups to make new derivatives. Manipulations like deoxygenation and the reduction of the ester function to an alcohol or reduction to and then further oxidation to an aldehyde or hemiacetal are all well known to one of skill in the art.

### ***Conclusion***

Claims 1-6 are rejected

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period

Art Unit: 1623

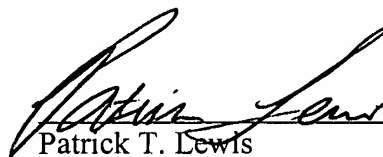
will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK

  
Patrick T. Lewis  
Primary Patent Examiner  
Art Unit 1623